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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

First Named Inventor	: Wenda C. Carlyle	Appeal No. ---
Appln. No.:	09/186,810	
Filed :	November 5, 1998	Group Art Unit: 3738
For :	MEDICAL DEVICES WITH ASSOCIATED GROWTH FACTORS	Examiner: Paul B. Prebilic
Docket No.:	S16.12-0052	

TRANSMITTAL OF APPEAL BRIEF
(PATENT APPLICATION - 37 C.F.R. §41.37)

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I HEREBY CERTIFY THAT THIS PAPER IS BEING SENT BY U.S. MAIL, FIRST CLASS, TO THE COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450, THIS 27 DAY OF February, 2007.

Hallie A Finucane
PATENT ATTORNEY

Sir:

Transmitted herewith is the Appeal Brief in this application with respect to the Notice of Appeal filed on December 27, 2006.

FEE STATUS

[---] Small entity status under 37 C.F.R. §§ 1.9 and 1.27 is established by a verified statement.

FEE FOR FILING APPEAL BRIEF

Pursuant to 37 C.F.R. §41.20(b)(2) the fee for filing the Appeal Brief is $500.00.

The Director is authorized to charge any additional fees associated with this paper or credit any overpayment to Deposit Account No. 23-1123. A duplicate copy of this communication is enclosed.

Respectfully submitted,
WESTMAN, CHAMPLIN & KELLY, P.A.

By: Hallie A Finucane

Hallie A. Finucane, Reg. No. 33,172
900 Second Avenue South, Suite 1400
Minneapolis, Minnesota 55402-3319
Phone: (612) 334-3222 Fax: (612) 334-3312

HAF:tlr

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First Named Inventor :	Wenda C. Carlyle	
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BRIEF FOR APPELLANT

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27 DAY OF February, 2007.

Hallie A Finucane

PATENT ATTORNEY

Dear Sir:

This Brief is presented in support of the Notice of Appeal filed December 27, 2007, from the final rejection of claims 1, 3, 4, 8-10, 13, 15, 34, 35, 38-40, 45 and 46 of the above-identified application, as set forth in the Office Action mailed October 27, 2006.

I. REAL PARTY OF INTEREST

The Real Party of Interest, St. Jude Medical, Inc., a corporation organized under the laws of the state of Minnesota, and having offices at One Lillehei Plaza, St. Paul, MN 55117, has acquired the entire right, title and interest in and to the invention, the application, and any and all patents to be obtained therefor, as set forth in the Assignment filed with the patent application and recorded on Reel 9595, Frame 0740.

II. RELATED APPEALS AND INTERFERENCES

An Appeal was filed on January 17, 2006 for U.S Patent Application Serial No. 09/014,087. The present application is a continuation-in-part of U.S Patent Application Serial No. 09/014,087.

III. STATUS OF CLAIMS

I.	Total number of claims in the application.		
		Claims in the application are:	1-46
II.	Status of all the claims.		
	A.	Claims cancelled:	2, 5-7, 11-12, 16-27 and 30-32
	B.	Claims withdrawn but not cancelled:	None
	C.	Claims pending:	1, 3, 4, 8-10, 13-15, 28, 29 and 33-46
	D.	Claims allowed:	28, 29, 33 and 41-44
	E.	Claims rejected:	1, 3, 4, 8-10, 13, 15, 34, 35 and 38-40, 45 and 46
	F.	Claims Objected to:	14, 36 and 37
III.	Claims on appeal		
		The claims on appeal are:	1, 3, 4, 8-10, 13, 15, 34, 35 and 38-40, 45 and 46

IV. STATUS OF AMENDMENTS

No amendment was filed subsequent to the final rejection.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The Applicants' invention in independent claim 1 is directed to a biomedical device comprising a natural tissue and a polypeptide growth factor associated with the natural tissue by a covalent bond using crosslinking agents. (at least page 7, line 31 - page 8, line 14, and page 16, lines 22 - page 17, line 15). Other associations that are used to attach the polypeptide growth factor to the natural tissue include antibody-antigen associations, specific binding protein-receptor associations, or enzyme-substrate associations. (at least page 16, lines 26-31, and page 18, lines 29-30). The crosslinking agent includes at least two aldehyde functional groups that form covalent bonds to link the crosslinking agent directly with the polypeptide growth factor and the natural tissue. (at least page 17, lines 5-15). The polypeptide growth factor associated with the natural tissue is effective to stimulate association of viable cells with the natural tissue. (at least page 7, lines 3-12, and page 10, lines 20-28).

The Applicants' invention in independent claim 45 is directed to a biomedical device comprising a biological matrix and a polypeptide growth factor crosslinked to the biological matrix by covalent bonding using crosslinking agents. (at least page 7, lines 15-20, page 8, line 15 – page 10, line 18, and page 16, lines 22-26). The crosslinking agent includes at least two aldehyde functional groups that form covalent bonds to link the crosslinking agent directly with the polypeptide growth factor and the biological matrix. (at least page 17, lines 5-15). The polypeptide growth factor associated with the biological matrix is effective to stimulate association of viable cells with the biological matrix. (at least page 7, lines 3-12, and page 10, lines 20-28).

Applicants' invention in independent claim 46 is directed to a prosthesis that includes a substrate, the substrate not including a linker molecule, and a polypeptide growth factor crosslinked to the substrate by covalent bonding using crosslinking agents. (at least page 7, line 14 – page 10, line 18, and page 16, line 22 - page 17, line 15). The cross-linking agents include at least two aldehyde functional groups that form covalent bonds to link the crosslinking agent directly with the polypeptide growth factor and the substrate. (at least page 17, lines 5-15). The polypeptide growth factor associated with the substrate is effective to stimulate association of viable cells with the substrate. (at least page 7, lines 3-12, and page 10, lines 20-28).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether Claim 46 is properly rejected under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement.

B. Whether Claim 46 is properly rejected under 35 U.S.C. §112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

C. Whether claims 1, 8, 10, 13, 15, 34, 35 and 38-40 are properly provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 9, 14 and 21 of copending Application No. 09/014,087.

D. Whether claims 1, 3, 4, 8, 9, 15, 45 and 46 are properly rejected as being anticipated by Cahalan et al., U.S. Patent No. 5,308,641 ("Cahalan patent").

E. Whether claim 10 is properly rejected as being unpatentable over the Cahalan patent in view of Goldstein, U.S. Patent No. 5,613,982 ("Goldstein patent").

F. Whether claim 13 is properly rejected as being unpatentable over the Cahalan patent in view of Bayne et al., European Patent Application No. 0476983 ("Bayne application").

VII. ARGUMENT

A. The Examiner Erroneously Rejected Claim 46 Under 35 U.S.C. §112, First Paragraph, For Failing To Comply With The Written Description Requirement.

The Office Action erroneously rejected independent claim 46 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Office Action alleges that independent claim 46 contains subject matter which was not described in the specification in a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the Application was filed, had possession of the claimed invention. The Office Action states that there is no support for the preclusion of a linker molecule as now claimed. The Office Action also alleges that the claimed invention does not appear to be enabled since a linker molecule is necessary for the invention to work as disclosed since the covalent attachment of a crosslinking agent to the tissue requires attachment to some molecule of the tissue.

In the Response to Arguments section of the Office Action, the Examiner erroneously asserts that the crosslinking agent of the present invention is a type of linker molecule because it functions to link the biomolecule to the surface. The Response to Arguments section also states that preclusion of a linker molecule when covalent bonds are formed does not have original support.

Applicants respectfully disagree that independent claim 46 fails to comply with the written description under 35 U.S.C. §112, first paragraph. Applicants have disclosed linker molecules at least on p.18, line 29 - p.19, line 18 of the specification. Similarly, the Application also discloses that the polypeptide growth factor can be attached to the substrate with a crosslinking agent. *See* page 17, line 5 – page 18, line 2. Utilizing a crosslinking agent to attach a polypeptide growth factor to a substrate is clearly different from attaching a polypeptide growth factor to a substrate with a linker molecule. Contrary to the allegation in the Office Action, Applicants did have possession of using both a crosslinking agent, such as glutaraldehyde, and a linker molecule, such as antibodies, at the time the Application was filed.

With respect to the allegation in the Response to Arguments section that Applicants did not have possession of covalently bonding a polypeptide growth factor to a substrate utilizing a crosslinking agent, Applicants reference the following disclosure in the Application: "The chemical binding of the VEGF can involve covalent bonding to the surface of the substrate with reactive agents such as glutaraldehyde and other general crosslinking agents. A typical procedure for chemical binding of VEGF to the surface of a tissue makes use of glutaraldehyde, which crosslinks proteins by way of two aldehyde groups. Since glutaraldehyde is typically used for fixation of some biocompatible materials, the non-specific crosslinking to bind the VEGF to the biocompatible material can be performed simultaneously with fixation of the tissue." *See* Page 17, lines 5-15 of the Application.

Therefore, there is clear support for the claimed subject matter and the preclusion of a linker molecule for attaching the polypeptide growth factor to the substrate in the Application. Further, a linker molecule has been disclosed in the specification as being a separate way of attaching a polypeptide growth factor to a substrate that is distinct from a crosslinking agent, such as glutaraldehyde or an epoxy.

Therefore, the rejection under 35 U.S.C. §112, first paragraph, is in error. Applicants respectfully request that the rejection of claim 46 under 35 U.S.C. §112, first paragraph, be reversed.

B. The Examiner Erroneously Rejected Claim 46 Under 35 U.S.C. §112, First Paragraph, For Failing To Comply With The Written Description Requirement.

The Office Action also erroneously rejected independent claim 46 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Office Action alleges that the preclusion of a linker molecule in independent claim 46 is confusing and renders the claimed language indefinite in that a molecule on the tissue must link to the crosslinking agent to bond it thereto. The Office Action also alleges that a crosslinking molecule is used as or acts as a linker molecule so the preclusion of it is confusing.

Applicants respectfully submit that claim 46 does particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants are allowed to claim negative limitations. *See* MPEP § 2173.05(i). As previously stated in section VII.A of this appeal brief, Applicants have disclosed numerous methods for attaching a polypeptide growth factor to a substrate. Applicants are thereby allowed to explicitly exclude methods of connecting a polypeptide growth factor to a natural substrate. "If alternative elements are positively recited in the specification, they may be explicitly excluded from the claims." *See In Re Johnson* 558 F.2d 1008, 1019, 194 U.S.P.Q. 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily describes the part remaining.").

Further, Applicants do not understand the Examiner's allegation that the crosslinking molecule is used as or acts as a linker molecule which causes the preclusion to be confusing. As previously stated, Applicants have disclosed different approaches of connecting the polypeptide growth factor to the substrate. One approach includes utilizing linker molecules and another approach includes utilizing crosslinking agents. The specification delineates between the two approaches and, therefore, there is no confusion as to the scope of the claim in light of the specification.

As such the Examiner erred in rejecting claim 46 for failure to comply with 35 U.S.C. §112, second paragraph. Applicants respectfully request that the rejection of claim 46 for failure to comply with 35 U.S.C. § 112, second paragraph, be reversed.

C. Whether claims 1, 8, 10, 13, 15, 34, 35 and 38-40 are properly provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 9, 14 and 21 of copending Application No. 09/014,087.

The Office Action also provisionally rejected claims 1, 8, 10, 13, 15, 34, 35, and 38-40 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 9, 14, and 21 of copending Application No. 09/014,087. Applicants have previously submitted that upon allowance of both the present Application and Application No. 09/014,087, Applicants will file a terminal disclaimer. Therefore, Applicants respectfully submit that the obviousness-type

double patenting rejection will be made moot by the submission of a terminal disclaimer in the event that both copending applications are in condition for allowance.

D. The Office Action Erred in Alleging that Claims 1, 3, 4, 8, 9, 15, 45 and 46 Are Anticipated by the Cahalan Patent.

The Office Action erroneously rejected independent claim 1 as being anticipated by the Cahalan patent. The Office Action alleges that the Cahalan patent anticipates independent claim 1 because the Cahalan patent allegedly discloses natural tissue as claimed and the crosslinking agent as claimed are the combination of the crosslinking agent of dialdehydes and the polyalkylimine of Cahalan. The Office Action alleges that the molecules are joined to form a crosslinking agent that attaches the polypeptide growth factor to the substrate. The Office Action alleges that Cahalan discloses that one purpose of the surface treatment is to promote the attachment and growth of a normal cell layer. The Office Action concludes that the Cahalan patent discloses a stimulation of "the association of viable cells with the substrate" as claimed.

In the Response to Arguments section of the Office Action, the Examiner erroneously asserted that since the two molecules of polyalkylimine and aldehyde are used together to surface bond the biomolecule, it is permissible to call the molecules together crosslinking agents. The Office Action continues that this is due to the fact that these molecules function to crosslink the surface and attach the biomolecule so they together function as a crosslinking agent. The Examiner then alleges that the claim was given its broadest reasonable interpretation.

Applicants respectfully disagree that the Cahalan patent anticipates independent claim 1. To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, all claim elements, and their limitations, must be found in the prior art reference to maintain a rejection based on 35 U.S.C. §102. During patent examination, the pending claims must be "given their broadest reasonable interpretation consistent

with the specification." *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach. *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999)

"[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, *i.e.*, as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 376 F.3d 1382, 75 USPQ2d 1321 (Fed. Cir. 2005) (*en banc*). It is the use of the words in the context of the written description and customarily by those skilled in the relevant art that accurately reflects both the "ordinary" and the "customary" meaning of the terms in the claims. *Ferguson Beauregard/Logic Controls v. Mega Systems*, 350 F.3d 1327, 1338, 69 USPQ2d 1001, 1009 (Fed. Cir. 2003).

Applicants submit that the Office action has taken an impermissibly broad interpretation of the disclosure of the Cahalan patent in alleging that polyalkylimine is a crosslinking agent. Referring to the abstract, the Cahalan patent states as follows: "An improved spacer material for improving the biocompatibility of a biomaterial and a method for making it in which a polyalkylimine is covalently attached to an aminated substrate and combined with a crosslinking agent which is at least difunctional in aldehyde groups." The Cahalan patent defines what is considered as a crosslinking agent at col. 4, lines 58-62. "The crosslinking agent employed in the present invention can be any crosslinking agent which is at least difunctional in aldehyde groups. For example, glutaraldehyde, glyoxal, malonaldehyde, succinaldehyde, adipaldehyde, and dialdehyde starch could be used." There is no disclosure that polyalkylimine is a crosslinking agent.

It is inconsistent with the disclosure of Cahalan to allege that polyalkylimine is a crosslinking agent when polyalkylimine is specifically disclosed as a spacer separate and apart from the crosslinking agent which is defined as being at least difunctional in aldehyde groups. The Cahalan patent clearly discloses that a crosslinking agent is at least difunctional in aldehyde groups. Polyalkylimine does not have aldehyde groups. Therefore, it is not understood how the Office Action could allege that polyalkylimine is a part of a crosslinking agent.

To further illustrate the point, referring to claim 1 of Cahalan, at col. 8, lines 25-34, Cahalan did not consider polyalkylimine to be a crosslinking agent in its claims when it distinctly claims a crosslinking agent separate from polyalkylimine. The same holds true for claim 4 and claim 15.

Just as the Cahalan patent distinguishes polyalkylimine from a crosslinking agent, the present application discloses what is considered as a crosslinking agent at least on page 6, lines 25-27, page 8, line 30 – page 9, line 3 and page 17, lines 5-21. Applicants disclose crosslinking agents as being glutaraldehyde, formaldehyde, other difunctinal aldehydes and epoxies. There is no disclosure that a spacer, such as polyalkylimine, could be considered to be a crosslinking agent by one of skill in the art.

Therefore, the Office Action erred in rejecting claim 1 as being anticipated by the Cahalan patent. Applicants respectfully request that the rejection of claim 1 be reversed.

The Office Action also erroneously rejected claims 3, 4, 8, 9 and 15 as being anticipated by the Cahalan patent. Claims 3, 4, 8, 9 and 15 depend from independent claim 1. While Applicants do not acquiesce to the rejection of any of the dependent claims, the rejection is in error in light of the fact that independent claim 1 is in allowable form. Reversal of the anticipation rejection of claims 3, 4, 8, 9 and 15 is respectfully requested.

The Office Action also rejected independent claim 45 as being anticipated by the Cahalan patent for the reasons cited above with respect to independent claim 1. Applicants respectfully disagree that the Cahalan patent anticipates independent claim 45 because claim 45 includes crosslinking agents comprising at least two aldehyde functional groups that form covalent bonds to link the crosslinking agent directly with the polypeptide growth factor and the biological matrix. For the reasons stated above with respect to independent claim 1, the Cahalan patent cannot be interpreted to include polyalkylimine as a crosslinking agent. Further, polyalkylimine does not have two functional aldehyde groups which covalently bond a polypeptide growth factor to a biological matrix. There is also no disclosure of a biological matrix being used as a substrate in Cahalan.

Therefore, the Cahalan patent does not disclose each and every element of independent claim 45, and therefore, does not anticipate independent claim 45. Reversal of the anticipation rejection of claim 45 is respectfully requested.

The Office Action also erred in rejecting independent claim 46 as being anticipated by the Cahalan patent for the reasons cited above with respect to independent claim 1. Claim 46 is directed to a prosthesis comprising a substrate, the substrate not including a linker molecule attached thereto, and a polypeptide growth factor crosslinked to the substrate by covalent bonding using crosslinking agents. Claim 46 states that the crosslinking agent comprises at least two aldehyde functional groups that form covalent bonds to link the crosslinking agent directly with the polypeptide growth factor and the substrate.

There is no disclosure of directly linking a polypeptide growth factor to a substrate as claimed in claim 46 in the Cahalan patent with a crosslinking agent comprising at least two aldehyde functional groups. Rather, the Cahalan patent discloses the use of a spacer namely, polyalkylimine, which cannot be considered to be a crosslinking agent as defined in the Cahalan patent for the reasons stated above with respect to claim 1. Further, polyalkylimine does not include at least two functional aldehyde groups as claimed for a crosslinking agent.

Therefore, claim 46 is not anticipated by the Cahalan patent. Reversal of the anticipation rejection of claim 46 is respectfully requested.

E. The Office Action Erred in Alleging That Claim 10 Is Made Obvious Over the Cahalan Patent in View of the Goldstein Patent.

The Office Action also erred in rejecting dependent claim 10 as being obvious over the Cahalan patent in view of the Goldstein patent. The Office Action alleges that the Cahalan patent discloses medical devices/implants where the crosslinking agent glutaraldehyde attaches the growth factor biomolecule and the substrate-spacer. The Office Action alleges that the solid surface disclosed in the Cahalan patent can be made of human or animal tissues, but Cahalan lacks the types of tissues claimed. The Office Action alleges that the Goldstein patent teaches that it was known to make similar medical devices/implants out of heart valves, pericardial

tissue and the like. The Office Action concludes that it would have been obvious to use heart valve or pericardial tissue for Cahalan's solid surface in order to reduce the risk of disease transmission and cost over using human tissue. The Office Action also alleges that it would have been obvious to use these tissues for the reasons that Goldstein desires the same.

Applicants respectfully disagree that claim 10 is made obvious by the combination of the Cahalan patent in view of the Goldstein patent. The Cahalan patent does not disclose a biomedical device comprising natural tissue and a polypeptide growth factor associated with the natural tissue by covalent bonding using crosslinking agents for the reasons stated above with respect to claim 1. The Goldstein patent does not cure the deficiencies of the Cahalan patent. Therefore, claim 10 is not made obvious as erroneously alleged by the Offfice Action. Reversal of the obviousness rejection of claim 10 is respectfully requested.

F. The Office Action Erred in Alleging that Claim 13 is Obvious Over the Cahalan Patent in View of the Bayne Application.

The Office Action also erred in rejecting dependent claim 13 as being obvious over the Cahalan patent in view of the Bayne application. The Office Action states that the Cahalan patent fails to disclose the use of VEGF as claimed even though it discloses utilizing many other growth factors therewith. The Office Action alleges that that the Bayne application teaches that it was known to use VEGF as the growth factor in a similar fashion within the same art. The Office Action concludes that it would have been obvious to an ordinary artisan to use VEGF as the growth factor of the Cahalan patent so that the implant could be successfully implanted in vascular regions of the body.

Applicants respectfully disagree that claim 13 is made obvious by the combination of the Cahalan patent in view of the Bayne application. The Cahalan patent does not disclose a biomedical device comprising natural tissue and a polypeptide growth factor associated with the natural tissue by covalent bonding using crosslinking agents for the reasons stated above with respect to claim 1. The Bayne application does not cure the deficiencies of the Cahalan patent. Therefore, claim 13 is

not made obvious, as erroneously alleged by the Offfice Action. Reversal of the obviousness rejection of claim 13 is respectfully requested.

Conclusion

Appellants respectfully submit that claims 1, 3, 4, 8-10, 13, 15, 34, 35, 38-40, 45 and 46 are patentable over the cited prior art and the statutory rejection of claim 46. It is respectfully requested that the rejections be reversed, and that all pending claims be allowed.

Respectfully submitted,

WESTMAN, CHAMPLIN & KELLY, P.A.

By: Hallie A Finucane

Hallie A. Finucane, Reg. No. 33,172
Suite 1400
900 Second Avenue South
Minneapolis, Minnesota 55402-3319
Phone:(612) 334-3222 Fax:(612) 334-3312

Appendix A

CLAIMS INVOLVED IN APPEAL:

1. (Previously Presented) A biomedical device comprising a natural tissue and a polypeptide growth factor associated with the natural tissue by covalent bonding using crosslinking agents, antibody-antigen associations, specific binding protein-receptor associations or enzyme-substrate associations, wherein the crosslinking agents comprise at least two aldehyde functional groups that form covalent bonds to link the crosslinking agent directly with the polypeptide growth factor and the natural tissue, the polypeptide growth factor associated with the natural tissue being effective to stimulate association of viable cells with the substrate.

3. (Previously Presented) The biomedical device of claim 1 wherein the crosslinking agent comprises difunctional aldehydes.

4. (Previously Presented) The biomedical device of claim 3 wherein the difunctional aldehyde comprises glutaraldehyde.

8. (Previously Presented) The biomedical device of claim 1 wherein the natural tissue comprises xenograft or homograft tissue.

9. (Previously Presented) The biomedical device of claim 1 wherein the natural tissue comprises human tissue.

10. (Previously Presented) The biomedical device of claim 1 wherein the natural tissue is selected from the group consisting of porcine tissue, bovine tissue, kangaroo tissue, canine tissue and a combination thereof.

13. (Previously Presented) The biomedical device of claim 1 wherein the polypeptide growth factor comprises vascular endothelial growth factor.

15. (Previously Presented) The biomedical device of claim 1 wherein the biomedical device comprises an artificial organ, a heart valve prosthesis, an annuloplasty ring, a stent, a pledget, suture, an electrical lead, a permanently in-dwelling percutaneous device, an AV shunt, a vascular graft, a dermal graft or a surgical patch.

34. (Previously Presented) A biomedical device comprising a substrate and a polypeptide growth factor associated with the substrate by antibody-antigen associations, specific binding protein-receptor associations or enzyme-substrate associations, the polypeptide growth factor associated with the substrate being effective to stimulate association of viable cells with the substrate.

35. (Previously Presented) The biomedical device of claim 34 wherein the biocompatible substrate comprises tissue.

38. (Previously Presented) The biomedical device of claim 34 wherein the polypeptide growth factor is associated with the substrate by antibody-antigen associations.

39. (Previously Presented) The biomedical device of claim 34 wherein the polypeptide growth factor is associated with the substrate by specific binding protein-receptor associations.

40. (Previously Presented) The biomedical device of claim 34 wherein the polypeptide growth factor is associated with the substrate by enzyme-substrate associations.

45. (Previously Presented) A biomedical device comprising a biological matrix and a polypeptide growth factor crosslinked to the biological matrix by covalent bonding using crosslinking agents, wherein the crosslinking agents comprise at least two aldehyde functional groups that form covalent bonds to link the crosslinking agent directly with the polypeptide growth factor and the biological matrix, the polypeptide growth factor associated with the biological matrix being effective to stimulate association of viable cells with the substrate.

46. (Previously Presented) A prosthesis comprising a substrate, the substrate not including a linker molecule attached thereto, and a polypeptide growth factor crosslinked to the substrate by covalent bonding using crosslinking agents, wherein the crosslinking agents comprise at least two aldehyde functional groups that form covalent bonds to link the crosslinking agent directly with the polypeptide growth factor and the substrate, the polypeptide growth factor associated with the substrate being effective to stimulate association of viable cells with the substrate.

Appendix B

Evidence Index

Applicant has submitted no evidence under 37 C.F.R. §§ 1.130, 1.131 or 1.132 through the prosecution of this application.

Appendix C

Related Proceedings Index

None.